ASSOCIATION OF FIRST TRIMESTER URIC ACID A PREDICTOR OF GDM

Dissertation submitted in partial fulfilment of the

Requirement for the award of the Degree of

M.S. DEGREE – BRANCH VI

OBSTETRICS AND GYNAECOLOGY

APRIL 2017

TIRUNELVELI MEDICAL COLLEGE HOSPITAL

THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY,

CHENNAI,

TAMIL NADU

CERTIFICATE

This is to certify that the Dissertation entitled "**ASSOCIATION OF FIRST TRIMESTER URIC ACID A PREDICTOR OF GDM**" submitted by DR. JEMIMAH J S M.S [Obstetrics and gynaecology]., to The Tamilnadu Dr.M.G.R. Medical University, Chennai, in partial fulfilment for the award of M.S (Obstetrics and Gynaecology) is a bonafide work carried out by her under my guidance and supervision during the academic year 2014-2017. This dissertation partially or fully has not been submitted for any other degree or diploma of this university or other.

GUIDE
Prof.Dr.Ramalakshmi, MD., DGO,
Department Obstetrics and Gynaecology,
Tirunelveli Medical College,
Tirunelveli- 627011.

HOD
Prof.Dr.MEENA,MD.,DGO.,DNB.,
Department Obstetrics and Gynaecology,
Tirunelveli Medical College,
Tirunelveli- 627011.

Dr.K.Sithy Athiya Munavarah,
THE DEAN,
Tirrunelveli Medical College,
Tirunelveli- 627011.

DECLARATION

I, DR.J S JEMIMAH., solemnly declare that the Dissertation titled **"ASSOCIATION OF FIRST TRIMESTER URIC ACID A PREDICTOR OF GDM"** had been prepared by me under the expert guidance and supervision of **Prof. Dr. Ramalakshmi MD., DGO.,** Professor, Department of Obstetrics and Gynaecology, Tirunelveli Medical College Hospital, Tirunelveli.

The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the regulation for the award of M.S. Degree (Branch VI) in Obstetrics and Gynaecology.

It was not submitted to the award of any degree/diploma to any University either in part or in full previously.

Place: Tirunelveli.
Date:

Dr. JEMIMAH J S M.S [obstetrics and Gynaecology]
POST GRADUATE,
M.S. (Obstetrics and Gynaecology),
Tirunelveli Medical College,
Tirunelveli.

TIRUNELVELI MEDICAL COLLEGE

INSTITUTIONAL RESEARCH ETHICS COMMITTEE
TIRUNELVELI, STATE OF TAMILNADU, SOUTH INDIA PIN 627011
91-462-2572719-EXT; 91-462-2572966; 91-462-2579785; 91-462-2572611-16
irmc@tvmc.ac.in, tirec@tvmc.ac.in; www.tvmc.ac.in

CERTIFICATE OF REGISTRATION & APPROVAL OF THE TIREC REF NO: 767/O&G/ 2015

PROTOCOL TITLE: ASSOCIATION OF FIRST TRIMESTER URIC ACID A PREDICTOR OF GDM

PRINCIPAL INVESTIGATOR: DR.J.S.JEMIMAH, MBBS.,

DESIGNATION OF PRINCIPAL INVESTIGATOR MS(O&G) POST GRADUATE IN OBSTETRICS & GYNAECOLOGY
DEPARTMENT & INSTITUTION: TIRUNELVELI MEDICAL COLLEGE , TIRUNELVELI

Dear , Dr.J.S.Jeminah, MBBS., The Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on 10.12.15.

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1. TIREC Application Form ☐
2. Study Protocol ☐
3. Department Research Committee Approval ☐
4. Patient Information Document and Consent Form in English and Vernacular Language ☐
5. Investigator's Brochure ☐
6. Proposed Methods for Patient Accrual Proposed ☐
7. Curriculum Vitae of the Principal Investigator ☐
8. Insurance /Compensation Policy ☐
9. Investigator's Agreement with Sponsor ☐
10. Investigator's Undertaking ☐
11. DCGI/DGFT approval ☐
12. Clinical Trial Agreement (CTA) ☐
13. Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA) ☐
14. Clinical Trials Registry-India (CTRI) Registration ☐

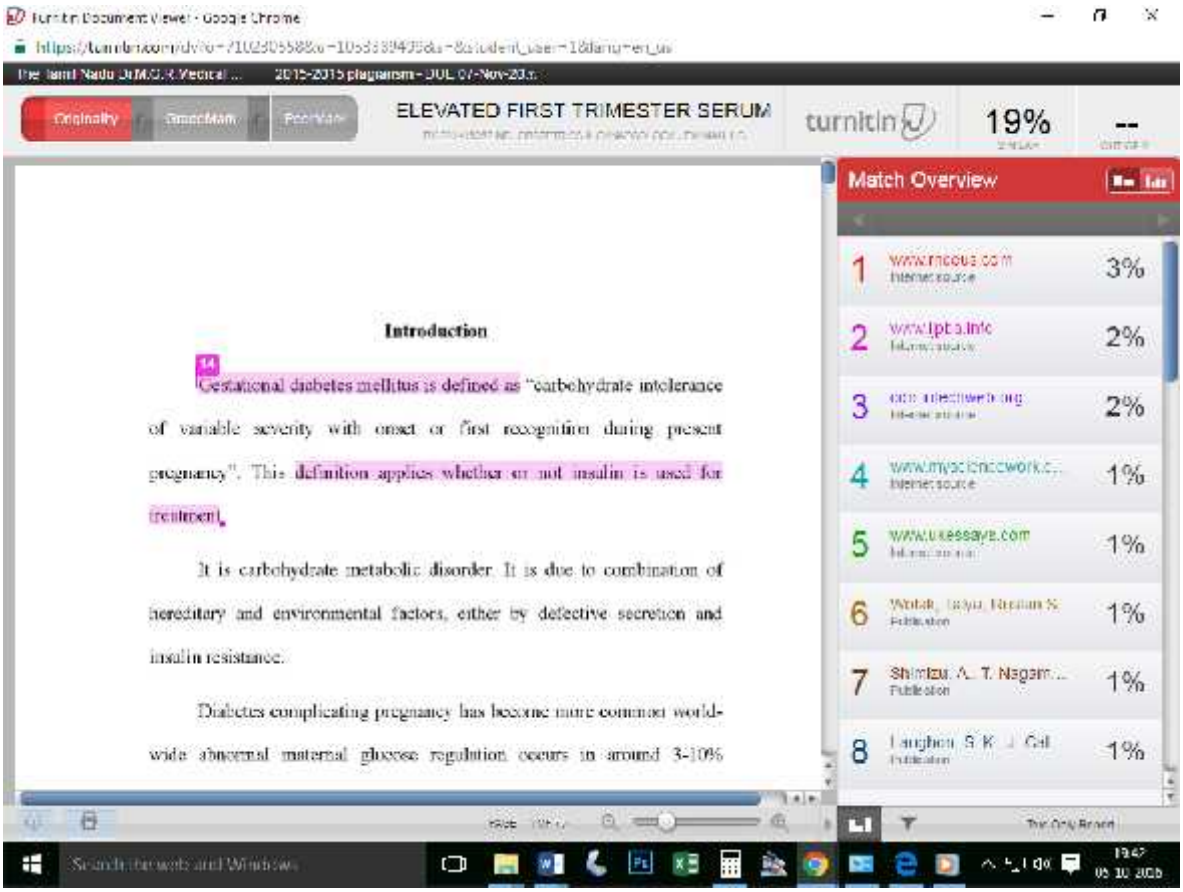
THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
6. At the time of PI's retirement/leaving the institute, the study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should receive the SAE reporting form within 24 hours of the occurrence.
8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented.
   d. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IEC, only then can they be implemented.
   e. Approval for amendment changes must be obtained prior to implementation of changes.
   f. The amendment is unlikely to be approved by the IEC unless all the above information is provided.
   g. Any deviation/violation/waiver in the protocol must be informed.

STANDS APPROVED UNDER SEAL

Dr.K.Shantaraman MD
Registrar, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
State of Tamilnadu, South India

Dr.V.Ramasubramanian MD DM
Member Secretary, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
State of Tamilnadu, South India



Introduction

Gestational diabetes mellitus is defined as "carbohydrate intolerance of variable severity with onset or first recognition during present pregnancy". This definition applies whether or not insulin is used for treatment.

It is carbohydrate metabolic disorder. It is due to combination of hereditary and environmental factors, either by defective secretion and insulin resistance.

Diabetes complicating pregnancy has become more common world-wide abnormal maternal glucose regulation occurs in around 3-10%

ACKNOWLEDGEMENT

I am very much thankful to the Dean **Dr. K.Sithy Athiya Munavarah**, Triunelveli Medical College Hospital, Tirunelveli, who has granted permission to do this study in this institution,

I take this opportunity to express my deepest sense of gratitude to professor **Dr.MEENA, M.D., DGO., DNB.,** Head of the Department of Obstetrics and Gynaecology, Tirunelveli Medical College Hospital, Tirunelveli for encouraging me and rendering timely suggestions and guiding me throughout the course of this study. simple words cannot express its for this contribution.

I am extremely thankful to my guide **Dr.RAMA LAKSHMI MD DGO .,**

I sincerely thank my professor **Dr.SHEBA ROSATTE VICTOR,M.D.,(OG)., Dr.M.SUJATHA ALAGESAN,M.D.,(OG),** for their support and guidance.

I am extremely thankful to all my **Assistant Professors** of the **Department of Obstetrics and Gynaecology** for their guidance and support throughout my study period in this institution.

Last but not the least, I am grateful to the antenatal mothers who willingly cooperated with me during the study

I thank all my colleagues and friends for their constant encouragement.

I extremely thankful to my family members

Above all I thank god almighty for his immense blessings

CONTENTS

S.No	TITLES	Page No
1.	Introduction	1
2.	Aim of the Study	3
3.	Review of Literature	4
4.	Materials and Methods	54
5.	Results	57
6.	Discussion	72
7.	Conclusion	77
8.	Bibliography	
9.	Proforma	
10.	Master Chart	
11.	Abbreviations	

Introduction

Gestational diabetes mellitus is defined as “carbohydrate intolerance of variable severity with onset or first recognition during present pregnancy”. This definition applies whether or not insulin is used for treatment.

It is carbohydrate metabolic disorder. It is due to combination of hereditary and environmental factors, either by defective secretion and insulin resistance.

Diabetes complicating pregnancy has become more common world-wide abnormal maternal glucose regulation occurs in around 3-10% pregnancies.

The reason for this rise in the prevalence of diabetes are mainly change in the life style, dietary habits older age at first conception poly cystic ovarian disease &obesity.

Uric acid is associated with insulin résistance in non pregnant women. In pregnancy uric acid is correlated with insulin resistance in women with gestational hypertension, and GDM . Uric acid is also higher in non-pregnant women with H/O GDM independent of body mass index.

Since insulin resistance is correlated with elevated uric acid we can predict the development of diabetes.

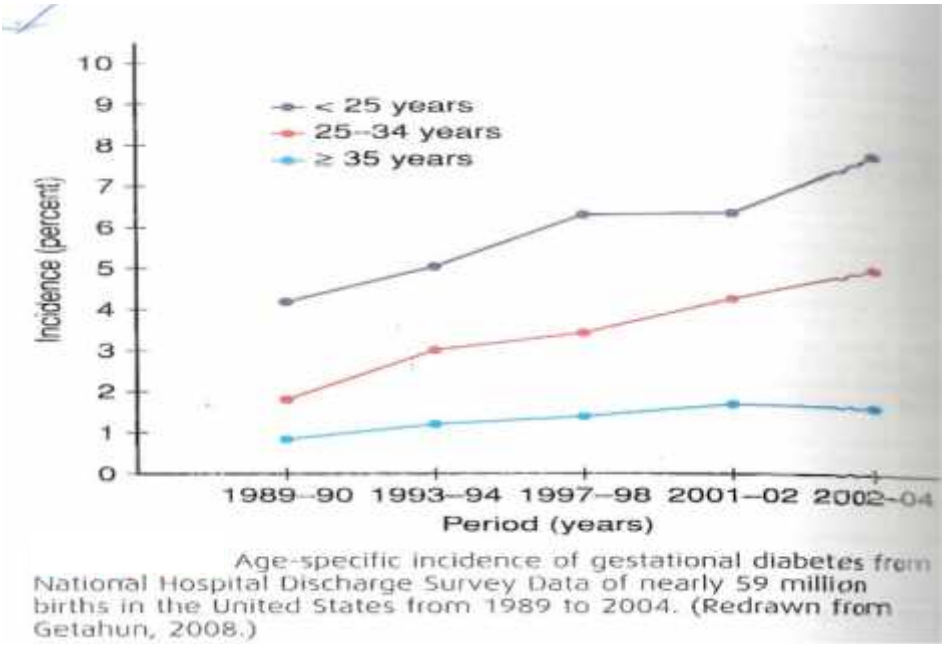
We hypothesis that elevated uric acid in the early weeks of gestation correlated with development of GDM.

Epidemiology of GDM

The incidence in world wide it is about 1-16% and is western 7% . The incidence varies based on the Criteria used to diagnose GDM, and the prevalence of type 2 Diabetes Mellitus and obesity in the population.

In Indian scenario the incidence is increasing from 2 % in 1981 to 16.5% in 2004.

The incidence of diabetes complicating pregnancy increased approximately 40% between 1989 and 2004 (Gestation 2008) African, American, Native American, Asian , Hispanic women are all high risk to get GDM



Age-specific incidence of gestational diabetes from National Hospital Discharge Survey Data of nearly 59 million births in the United States from 1989 to 2004. (Redrawn from Getahun, 2008.)

AIM OF THE STUDY

AIM:

To analyse the relationship between first trimester uric acid levels and prediction of developing gestational diabetes mellitus

REVIEW OF LITERATURE

PREVALENCE OF GDM

Globally, the quoted prevalence of GDM ranges from1-16% (Agarwal, Dhatt, Punnose &Koster,2005). This may be in part due to the different screening and diagnostic strategies employed to identify the condition and the particular population studied. The Australian Carbohydrate Intolerance Study(ACHOIS) undertaken in14centersin Australiaand4 centres in the United Kingdom reported that GDM affected 2-9% of all pregnancies (Crowtheretal, Hilleretal, Mossetal, McPheeetal, Jeffries & Robinsonetal,2005).Whilst, Tuffnelletal, Westetal and Walkinshaw et al (2003)in their systematic review of treatment for GDM and impaired glucose tolerance (IGT), for the 7 Cochrane Database state that 3-6% of all pregnancies are affected by GDM and IGT.

Terminology in the literature, relating to disturbances of carbohydrate metabolism in pregnancy can be confusing .In 1985,the World Health Organization (WHO) classification subdivided abnormal glucose tolerance in pregnancy into three categories defined by fasting venous glucose levels and venous plasma glucose values two hours after a 75 gram oral glucose load (Nordinetal, Weietal, Naingetal and Symonds et al, 2006).The three classifications were impaired fasting glucose(IFG),impaired glucose tolerance(IGT) and GDM. The revised WHO classification (1999) now defines GDM as any abnormal carbohydrate metabolism first recognized, or diagnosed in pregnancy, regardless of severity. Remnants of the earlier classification are still encountered in the literature.

PATHOGENESIS

Pregnancy is a unique physiological condition. It is a diabetogenic condition due to progressive increase in the insulin resistance.

The diabetogenic effects of pregnancy are:

1. Insulin resistance:
2. Increased lipolysis
3. Changes in gluconeogenesis
4. Uric acid causing insulin resistance

1.Insulin resistance:

a. Presence of human placental lactogen, cortisol, estriol, progesterone which all have anti insulin action.
b. Increased destruction of insulin by kidney and placenta (Insulinase)
c. Android obesity (Increase in Omental mesenteric fat.
d. α TNP impaired insulin signalling inhibits insulin receptor tyrosine kinase activity at the molecular level, there is decrease GLUT4 protein transporter.

2.Increased lipolysis

Glucose is used by the fetus lipolysis is increased in maternal side to meet caloric needs.

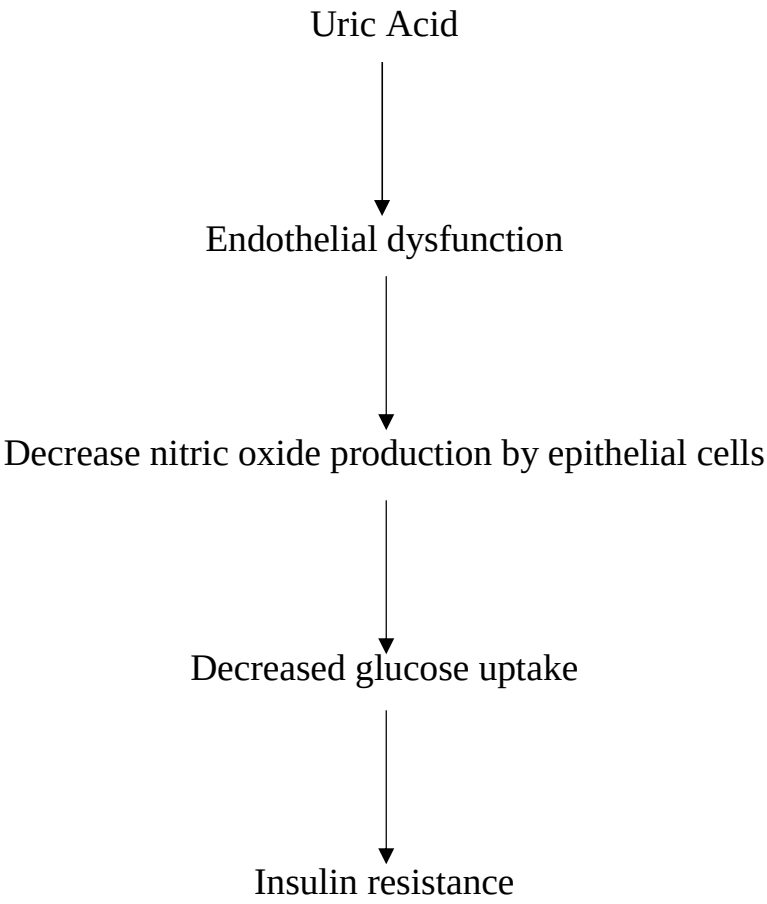
3.Changes in gluconeogenesis

Fetus utilizes energy that derived from alanine and other amino acids (Gluconeogenesis)

4.Uric acid causing insulin resistance

Two mechanism have been hypothesized by which uric acid can cause insulin resistance.

- Uric acid causes endothelial dysfunction and decrease Nitric oxide production by epithelial cells.
- Uric acid causes inflammation and oxidative stress in adipocytes



I. Nackagawa et al proposed that uric acid causes endothelial dysfunction and decreases nitricoxide production by the endothelial cells.

In animals insulins action on cellular glucose uptake of the skeletal muscle and adipose tissue is dependent on nitric oxide.

Thus decrease in nitric oxide lead to decreased glucose uptake and the development of insulin resistance.

II. Another mechanism by which uric acid may induce insulin resistance may be that uric acid cause inflammation and oxidative stress in adipocytes which is a contributor leads to metabolic syndrome.

Uric acid increase with increased protein intake alcohol consumption decreased excretion or increased endogenous production.

Maternal glucose homeostasis in pregnancy

Maternal glucose homoeostasis pregnancy is a condition of

I. Accelerated starvation
II. Facilitated anabolism
III. Hyper insulinism
IV. Insulin resistance

1. ACCELERATED STARVATION:

There is fasting hypoglycaemia because glucose is diverted to fetes by facilitated diffusion& increase insulin secretion during pregnancy, &amino acids diverted to fetus by active transport leads to substrate deficiency syndrome in the mother.

2. FACILITATED ANABOLISM:

There is prolonged hyperglycaemia after eating because of

- ❖ increase absorption from gut.
- ❖ delayed glucose exchange from blood
- ❖ decrease uptake by muscle and splanchnic tissues and
- ❖ decrease conversion to glycogen in liver.

3. HYPER INSULINISM

Increase in oestrogen and progestogen leads to

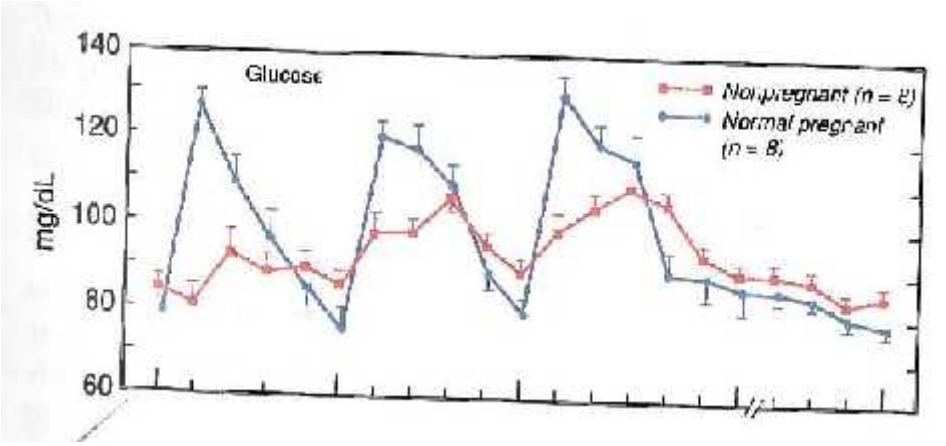
- ❖ B-cell hyperplasia there by leading to increase insulin secretion
- ❖ increase sensitivities of B-cells to glucose load
- ❖ increase suppression of glucose after meals.

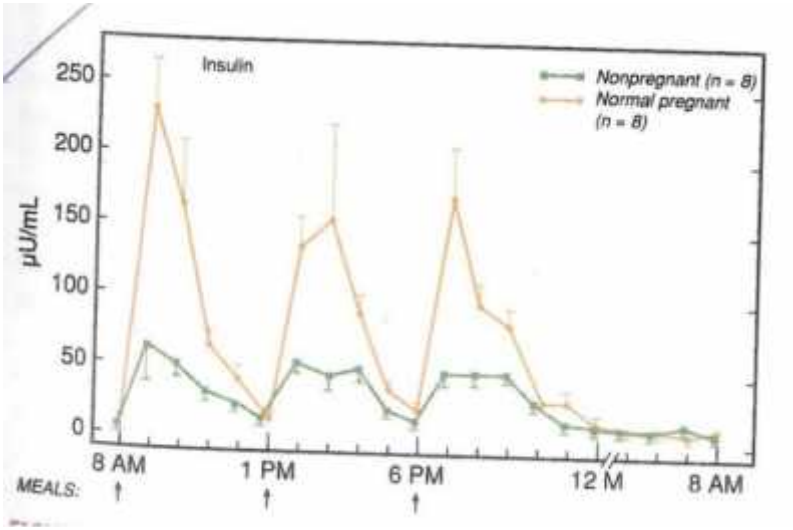
4.INSULIN RESISTANCE:

By hormones HPL, Prolactin’s

Diurnal Changes in Plasma Glucose and insulin in normal late pregnancy

.





Type of Diabetes:

I.ETIOLOGICAL CLASSIFICATION OF DIABETES MELLITUS

Type 1:

In type-1 diabetes there is absolute insulin deficiency due to complete β-Cell destruction.

- ❖ Immunological cause.
- ❖ idiopathic

Type 2:

Varies from only insulin resistance to insulin resistance or associated defective secretion.

Other types:

- ➢ Genetic mutations that alter β-Cell function leads to maturity onset diabetes of the young- 1-6, others
- ➢ Defective insulin action due to genetic cause.
- ➢ Genetic syndromes – Down, Klinefelter, Turner
- ➢ Diseases of the exocrine pancreas – pancreatitis, cystic fibrosis
- ➢ Endocrinopathies

Cushing syndrome,

Pheochromocytoma, others

- Drug or chemical induced

Glucocorticosteroids

Inhibit insulin action and stimulate gluconeogenesis resulting in hyperglycaemia.

Thiazides

Cause hypokalemia that will affect insulin secretion.

β-adrenergic agonists, others

- Infections – congenital rubella, cytomegalovirus

coxackievirus

Gestational diabetes

II.CLASSIFICATION DURING PREGNANCY:

1. Pregestational diabetes / overt
2. Gestational diabetes.

Those diagnosed during pregnancy Gestational diabetes

ACOG 1986 Classification

NDDG CLASSIFICATION

	NEW NAME	OLD NAME
TYPE I	IDDM	Juvenile diabetes
TYPE II	NIDDM	Adult onset
TYPE III		Gestational diabetes

AMERICAN COLLEGE OF OBSTETRICS & GYNAECOLOGY

Class	Onset	Fasting	2Hr PPBs	Therapy
A1	Gestational	<105m/d	<120m	Diet
A2	Gestational	>105m/d	>120m	Insulin
Class B-H similar to white is classification				

White classification in pregnancy

Until mid 1990. Priscilla white classification were followed today we use less frequently

White's Classification of diabetes during pregnancy

Gestational diabetes	Discovered during Pregnancy, glycemia may or may not be maintained by diet alone and insulin may be requires
Class A	Discovered before pregnancy, controlled with diet alone, any duration or age of onset
Class B	Onset age 20 years or older, duration less than 10 years
Class C	Onset age 10 -19 years, duration 10-19 years.
Class D	Onset age under 10 years duration over 20 years, background retinopathy.
Class R	Proliferative retinopathy or vitreous haemorrhage.
Class F	Nephropathy with proteinuria over 500mg/day
Class RF	Criteria for both class R and F coexist

Class H	Atherosclerotic heart disease clinically evident
Class T	Prior renal transplantation

Many now recommend adoption of the classification proposed by the **American Diabetes Association**

Proposed Classification system for Diabetes in Pregnancy	
Gestational diabetes: Diabetes diagnosed during pregnancy that is not clearly overt (type 1 or type 2) diabetes	
Type 1 Diabetes:	**Type 2 Diabetes:**
Diabetes resulting from β-Cell destruction, usually leading to absolute insulin deficiency a. Without vascular complication b. With vascular complications (Specify which)	Diabetes from inadequate insulin secretion in the face of increased insulin resistance a. Without vascular Complications b. With vascular complications (Specify which)
Other types of diabetes: genetic in origin, associated with pancreatic disease, drug – induced, or chemically induced	
Data from American Diabetes Association, 2012	

Screening of GDM

The best screening test should be sensitive, specific, simple, cheap and should be used conveniently, by screening of GDM we can prevent maternal & foetal adverse outcome, we can diagnosis small portions that are unrecognized pre-existing diabetes so that we can prevent micro vascular complication by early diagnosis &follow up. Because they are at increased risk of 50% Type 2 diabetes in 10 to 15 years.

In 2001 the ACOG:

Recommended universal screening for GDM by taking history, clinical risk factors or with a 50 gm one-hour loading test @24-28 weeks. They rely on the 100g 3 Hr OGTT for diagnosis. This is called as to as two step method.

The fifth international workshop conference on GDM (November 2005) endorsed continuation of the use of classification criteria and strategies for detections and diagnosis of GDM that were recommended @ fourth workshop conference.

Pregnant women can be classified as low, moderate or high risk based on various factors.

Low risk:

Screening of GDM not recommended routinely in these group,

- Those women had normal birthweight
- Who had normal weight before pregnancy
- Without history of glucose intolerance
- No family history of diabetes in first degree relative
- Who belongs to ethnic group where prevalence of GDM is low
- Age < 25 years

Moderate Risk:

One or more of the following in these women blood glucose testing be done 24-28 weeks (one or two step present)

- Weight high @ Birth
- Over weight prior to pregnancy
- Family history diabetes in first degree relative
- Who belongs to high prevalence ethnic group for GDM.

High risk:

In these women glucose testing should be done immediately possible

- Marked obesity
- Strong family history of type 2DM
- Presence of previous obstetric history of GDM or impaired glucose tolerance of glycosuria or macrosomia baby

The NICE guidelines of 2008

That screening for GDM be done using risk factors in a healthy population

- BMI> 30Kg/ sqm
- Previous baby > 4.5 Kg
- First degree relative with DM
- Ethnicity

The ADA (American Diabetic association and the IADPSG

Recommended the one step diagnostic 75g -2Hr OGTT

The cut – offs for this OGTT

FBS ≥ 92 mg /dl

Post 1 Hr ≥ 180 mg /dl

Post 2 Hr ≥ 153 mg/dl

The following algorithm was suggested combining the recommendation of the ADA and IAD PSG in 2011 for diabetes in pregnancy

1. Testing of all women the first antenatal visit < 13 weeks – early detection reduces complication.
2. Test women who have ANY risk factor.
    a) Non Caucasian
    b) BMI> 25 (a t risk BMI may be lower in some ethnic groups)
    c) Previous baby 4000 Gm > more
    d) History of GDM or prediabetes, unexplained still birth, malformed infant.
    e) Family history of diabetes in first degree relative.
    f) Glycosuria
    g) Drugs that increased blood glucose level
    h) Polycystic ovarian syndrome cardiovascular disease, hypertension, hyperlipidemia.

Screening Test

Glucose challenge Test:

(O Sullivan Test)

The glucose challenge test is performed by administering 50 gm of anhydrous glucose orally irrespective of time of the day previous meal. Venous blood glucose is then measured 1 Hr later plasma glucose level is >140 mg/dl

3-Hr 100 gm of GTT is recommended.

Seshiah's spot test:

Plasma glucose estimation is done in relation to the last Meal critical valves

OHr	-	85mg%
½ Hr	-	95 mg%
1 Hr	-	105 mg%
2 Hr	-	105 mg%
2Hr	-	30mg%-95 mg%
3Hr	-	90 mg%

GTT

Gold standard test is the 3 Hrs 100 gm oral glucose tolerance test

The WHO has recommended the 75 gm of 2 Hr oral GTT which is often used in Europe.

In the US the 100gm 3 Hr GTT performed.

The patient should be

- After on over right fasting 8-10 Hrs (ACOG 2001)
- Unrestricted diet in the previous 3 days
- Should be ambulant
- Smoking should be avoided
- Stop drugs - phenytoin thiazides OC pills, steroids
- Post pone after 3 wks if major surgery/ stress

Procedure

After overnight fasting, fasting blood sugar is collected along with urine sugar.

100 gms of glucose is given. It can be dissolved with 200 ml of plain water or lime water to improve palatability. venous blood is drawn for 3 hours along with urine.

	O Sullivan & Mahan whole blood	NDDG Plasma	Cerpenters couston plasma	WHO	DIPSI 2006	IADPSG 2010
Glucose	100gm	100gm	100gm	75gm	75gm	75gm
Fasting	95	105	95	126		92
1Hr	165	190	180	-		180
2Hr	145	165	155	140	140	153
3Hr	125	145	140			

Fifth international workshop conference of Gestational Diabetes:

Diagnostic criteria of Gestational Diabetes by Oral Glucose

Tolerance Testing

Oral Glucose Load				
Time	**100-g Glucose [b]**		**75-g Glucose [b]**	
Fasting	95 mg/dL	5.3 mmol /L	95 mg/dL	5.3 mmol /L
1-hr	180 mg/dL	10.0 mmol /L	180 mg/dL	10.0 mmol /L
2-hr	155 mg/dL	8.6 mmol /L	155 mg/dL	8.6 mmol /L
3-hr	140 mg/dL	7.8 mmol /L	-	-

Two or more of the venous plasma glucose concentrations listed must be met or exceeded for a positive diagnosis. Data from Metzger, 2007.

SPECIAL TESTS

Intravenous Glucose tolerance test (GTT)

25 grams glucose in 50% solution is given IV over 3 minutes. Blood sample is collected every 10 minutes for 1 hour.

Graph of blood glucose against time plotted.

K (Constant) = 0.696 x 100/t ½.

t ½- Time taken for blood glucose to fall to 50% of the value at 10 minutes.

Normal- K= 1.2 TO 2.3 <1.2 – Diagnosed as GDM.

Advantages

Short duration

Useful in patients with Malabsorption syndromes.

Disadvantages

Frequent collection

Non physiological so only for research purposes.

Other screening test

1. Glycosuria
2. Instant blood glucose using strips & meters
3. HbA_1C
4. Serum fructosamine assay

I.Glycosuria:

Glycosuria on the second fasting urine is significant. Also glycosuria if associated with Ketonuria is significant Normally100 gm of glucose excreted per day.

It can be measured by benedict's Test→ +ve with are reducing sugars & with some drugs. So It is Non- Specific.

I. Clinstix test:

Specific for glucose

Disadvantage:

- Glycosuria is present is diabetes mellitus alimentary glycosuria, Renal glycosuria, Lactosuria.
- Differs from person to person and on various occasions.

- Blood sugar does not correlate with urine sugar always.

II. Instant blood glucose (CBG)

- Easy to perform
- Vere puncture not needed
- Quick results
- But lack precision

  Capillary blood glucose levels is 20 mg% higher than whole blood level,

III. Glycosylated HB (HBAIC)

- Reflects glycaemic control over last 2-3 months.

  Normal ranges 5-8%

  <8.5% - good control

  8.5-9.5 % fair control

  >9.5% - poor control

Variable values in renal failure reduced in anaemia hemoglobinopathies, and blood transfusion.

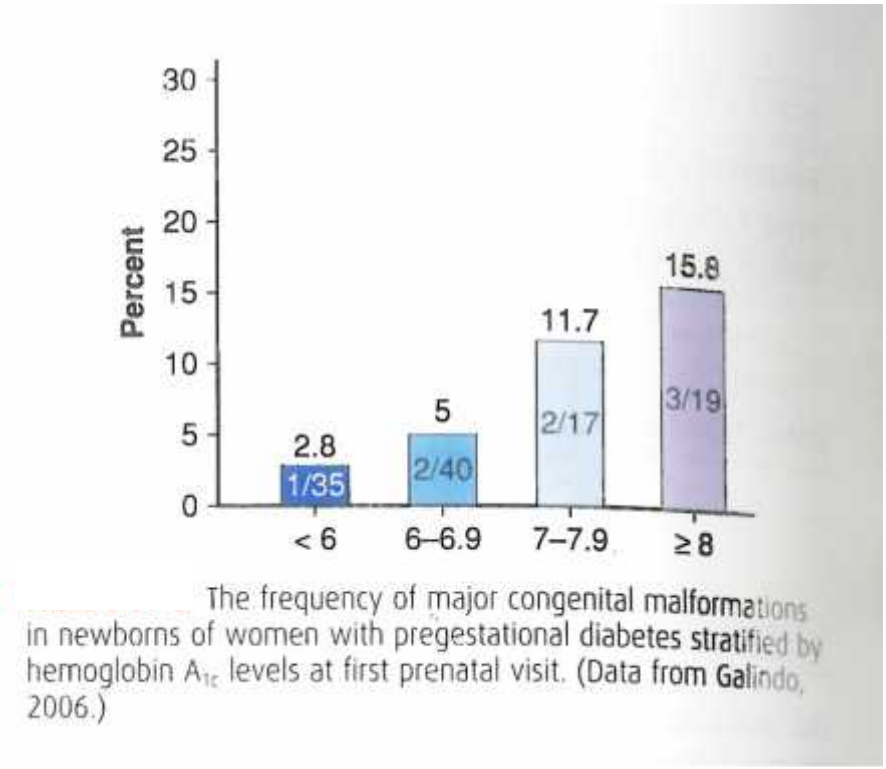
HbA_1C

- <7% No Greater risk for anomalies then non diabetic mother.
- 7-8.5% risk of 5% for anomalies >10% risk of anomalies rises to 22%
- Therapy must be for targeted to achieve a pre pregnancy

HbAIC	Risk of anomalies
7-8.5%	5%
10%	22%

HbAIC < 6.1 % (NICE Guidelines 2005)

It is >10% - avoid pregnancy



The frequency of major congenital malformations in newborns of women with pregestational diabetes stratified by hemoglobin A_{1c} levels at first prenatal visit. (Data from Galindo, 2006.)

IV. serum fructosamine assay:

- Reflects glycemic control over last 2 weeks.
- (N) valve up to 285 µmu/L
- Reliable in anaemia
- Costly test

To assess complications

- INVESTIGATIONS FOR ASSESSING GLYCAEMIC STATUS
- INVESTIGATIONS FOR ASSESSING COMPLICATIONS

To assess glycaemic status

1. In controlled GDM, DM, once in 2-4 weeks
2. Self-blood glucose monitoring is mandatory in all the pregnant women on insulin
3. Patients with fluctuating glucose levels
4. Patients showing recurrent ketosis or hypoglycaemic
5. In the perioperative period

INVESTIGATIONS FOR ASSESSING GLYCAEMIC STATUS:

- Urine sugar monitoring – unreliable.
- Blood sugar estimation is best.

In controlled GDM, DM, once in 2-4 weeks.

Self-blood glucose monitoring (SMBG) is mandatory in

- All the pregnant women on insulin
- Patients with fluctuating glucose levels.
- Patients showing recurrent ketosis or hypoglycaemia
- In the perioperative period.

INVESTIGATIONS FOR ASSESSING COMPLICATIONS

Infections

Asymptomatic bacteriuria to be looked for at booking, 28, 32, 36, weeks.

Vulvar moniliasis screening

Urine should be examined for proteins and microscopic deposits during each visit.

Diabetic nephropathy

- Urine for proteins using dipstick during each visits.
- If dipstick +ve 24 hours urinary protein for microalbuminuria.
- Renal function tests- blood urea, serum creatinine, serum electrolytes.

Diabetic retinopathy

- Measuring visual acuity
- Opthalmoscopic examination through dilated pupils stages

1. Non proliferative retinopathy
2. Preproliferative retinopathy

3. Proliferative retinopathy.

- ❖ Coronary heart disease and cardiomyopathy. ECG in all the leads and echocardiogram.
- ❖ Fasting lipid profile.
- ❖ Urine for ketone bodies and serum electrolytes in the presence of high blood sugar, persistent vomiting and infection.

Screening for fetal anomalies:

- ❖ Glycosylated Hb estimation.
- ❖ Chorionic villous sampling
- ❖ Maternal serum α fetoprotein estimation
- ❖ Amniocentesis
- ❖ Targeted ultrasound
- ❖ Fetal echocardiogram

Ultra sound

Assessment of altered growth

Ultrasound every 4 weeks form 20 weeks.

MACROSOMIA can be identified by

- AC and high diameter > 90^{th} percentile
- Head and femur measurements <90^{th} percentile.
- Abdominal girth > head circumference.
- AC change > 1-2 cm/ week.
- Increase subcutaneous fat.

For assessing amniotic fluid volume.

For assessing placental positon

ADVERSE OUTCOMES ASSOCIATED WITH GESTATIONAL DIABETES:

Maternal problems

Pregnancy:

- Anxiety
- Abnormal weight gain in pregnancy

- ❖ Preeclampsia
- ❖ Birth Trauma (Secondary to macrosomia)
- ❖ Increased rate of caesarean section
- ❖ Polyhydramnios
- ❖ Spontaneous abortion
- ❖ Preterm labour

Later life:

- ❖ Increased rate of type 2 DM in later life.
- ❖ 50% recurrence of GDM in 30-50%
- ❖ Increased rate of hypertension and cardio vascular disease

Problems in offspring (Fatal) neonatal / Adult life.

Fetal life:

- o Abortion
- o Malformation
- o Intra Uterine death
- o Macrosomia
- o Shoulder dystocia/ hypoxia
- o Acidosis / Erb's palsy

- Iatrogenic prematurity

Neonatal life:

- Hypoglycemia
- Polycythemia
- Hyperbilirubinemia
- Hypocalcemia
- Cardiomyopathy
- Respiratory Distress syndrome

Adult life:

Obesity

Increase rate of T2 DM in later life

Increased rate of hypertension end cardiovascular

Fetal macrosomia

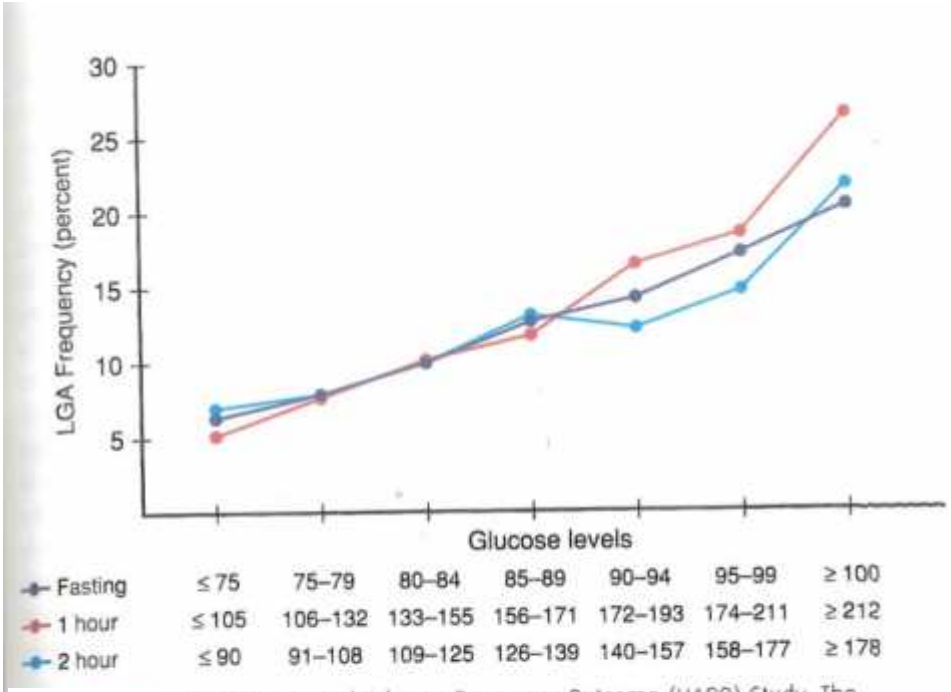
Maternal hyperglycaemia Stimulate fetal insulin secretion particularly during second half of pregnancy. This is turn leads to excessive somatic growth

The excessive shoulder & trunk fat that characterizes the macrosomia infant of diabetic mother predispose such infants to shoulder dystocia & caesarean section.

Insulin like growth factor also important in regulating fetal growth.

Leo and coworkers (2012) reported that there is positive evidence between insulin like growth factor and birth weight.

The **HAPO** study also reported dramatic increases of C- peptide levels with increasing maternal glucose level in macrosomia babies.



Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. The frequency of newborn birthweight ≥ 90th percentile for gestational age plotted against glucose levels (mg/dL) fasting and at 1- and 2-hr intervals following a 75-g oral glucose load. LGA = large for gestational age. (Adapted from The HAPO Study Cooperative Research Group, 2008.)

This 6050-g macrosomic infant was born
woman with diabetes

Other factors include epidermal growth factors, fibroblast growth factors, platelet derived growth factor, leptin, adiponectin.

Neonatal hypoglycaemia

Neonatal hyperinsulinemia may provoke hypoglycaemia within minutes of birth.

Newborns described by the HAPO study had an incidence of clinical neonatal hypoglycaemia that increased with increasing maternal OGTT values. Cord blood insulin levels are related to maternal glucose control.

Maternal obesity:

Torloni and coworkers (2009) estimated that gestational diabetes prevalence increase by approximately **1% for every 1Kg / m^2**increase in BMI

Weight distribution pattern also related to risk of getting gestational diabetes. In truncal obesity there is increased.

There is also evidence that increased maternal abdominal subcutaneous fat thickness at 18-22 weeks of GA correlated with BMI and It was a better predictor of gestational diabetes.

Excessive weight gain also identified in GDM

Congenital malformation

The cause for congenital malformation

- ❖ Inter related muscular chain reactions due to hyperglycemia
- ❖ Alteration in cellular lipid metabolism
- ❖ Excess production of toxic super oxide radicals
- ❖ Activation of programmed cell death

- ❖ Oxidative stress induced by hyperglycemia inhibits migration of cardiac neural crest cells.

Effects of Diabetes on Pregnancy

Maternal Effects:

1. **preeclampsia**

Pre-Eclampsia occurs is 10% of patient with GDM. It is more common in younger, nulliparous, obese, those who gain excessive weight gain during pregnancies.

The risk of superadded pre-eclampsia is around 35-60% in women who had micro albuminuria

Severity of these complications varies with the duration and severity of abnormal glucose levels.

2. **Acceleration of the end organ disease nephropathy.**

Stage 1:

Microalbuminuria (albumin to creatinine ratio >/=3.5 mg/ mmol or 24 hr urinary collection shows urine Albumin excretes of 20-199 micro /min or 30-299 mg / 2 Hr.

Stage 2:

Microalbuminuria (albumin to creatinine ratio >/=30 mg/ mmol or urinary albumin excretes of 200 mg/L or more.

Stage 3:

End stage Renal Disease

3. Risk of death due to cardiomyopathy
4. Other complications preterm labour, chroioammiontis polyhydramnios, UTI.

The steroids and tocolytics like β-Z agonists given in cases of preterm labour worsen hyperglycaemia and predispose to ketoacidosis

5. In case of uncontrolled diabetes prior to pregnancy risk of recurrent pregnancy loss increase.
6. Febrile illness' dehydration form hyperemesis or diarrhoeal disease can precipitate ketoacidosis which can be life ending also cause sudden fetal death
7. Increased need for hospital admission to either initiate insulin therapy or during inter current illness Emergency situation like preterm labour, diabetic ketoacidosis

8. There is a risk of worsening of end organ damage in nephropathy retinopathy , cardiovascular disease.
9. Neuropathy may manifest in the form of gastroparesis resulting in increasing gastric emptying time.
10. Renal disease develops 25-30/- women with insulin dependent diabetes of a l Background or mild non proliferative retinopathy should be screened follow up during pregnancy with a dilated fundus examination should be done.

Intrapartum there may be chances of infections, need for operative delivery either instrumental or caesarean section

In postpartum period there is risk of postpartum haemorrhage, infection puerperal sepsis.

Management

Diabetic Diet:

ADA recommends individualized nutritional counselling based on height and weight on average this includes daily calorie intake of 30 to 35 Kcal/kg. Total calorie constitutes 55%, Carbohydrate 20%, protein 25%, Fat (<10 saturated fat)

The ACOG 2013 suggests Carbohydrate intake limited to 40% of Total calorie

Exercise:

The ACOG (2013) include a moderate exercise program in the treatment plan of women with gestational diabetes

It can decrease the insulin requirement by 50 %

Glucose Monitoring:

There is evidence to support the common practice of blood glucose self-monitoring for women with diet treated gestational diabetes

The ACOG recommends four times daily glucose monitoring performed fasting and either 1 or 2 Hr after each meal.

Insulin Treatment:

The ACOG recommends that insulin be considered in women with 1Hr post prandial levels that persistently Levels that persistently exceed 140 mg/dl or those with 2-Hr levels above 120 mg/dl

The strong dose of insulin 0.7 -1.0 units /kg (ACOG) combination fo intermediate acting and short acting insulin may be used

Oral hypoglycaemic agent:

The ACOG acknowledge that both glyburide and metformin are appropriate for first line glycaemic control

Fifth international workshop – conference: Metabolic Assessments Recommended after pregnancy with gestational diabetes		
TIME	**TEST**	**PURPOSE**
Post-delivery(1- 3 d)	Fasting or random plasma glucose	Detect Persistent, Overt Diabetes
Early Postpartum (6-12 wk)	75- g, 2-hr hr OGTT	Postpartum classification of Glucose metabolism
1-Yr Postpartum	75-g, 2-hr OGTT	Assess glucose metabolism
Annually	Fasting plasma glucose	Assess glucose metabolism
Triannially	75-g, 2-hr OGTT	Assess glucose metabolism
Prepregnancy:	75-g, 2-hr OGTT	Classify glucose metabolism
Classification of the American Diabetes Association (2013)		
Normal Values	**Impaired Fasting Glucose or impaired glucose Tolerance**	**Diabetes Mellitus**
Fasting <100 mg /dl	100-125 mg/dl	≥ 126 mg /dl
2 hr < 140 mg /dl	2 hr ≥ 140 -199 mg/dl	2 hr ≥ 200 mg /dl
Hemoglobin A1c < 5.7 %	5.7 – 6.4%	≥ 6.5 %
OGTT= oral glucose tolerance test From American diabetes Association, 2013; Metzger, 2007.		

Uric acid

Uric acid is the end product of purine metabolism. Purines are obtained from both dietary sources, & from the breakdown of body protein liver kidneys sweet breads, sardines, anchovies spinach sources of purine.- they are all rich sources of purines

The Kidneys excrete two thirds of the uric acid produced daily. Remaining one third is excreted in the stool.

Uric acid level shows day to day, Seasonal variations in the same person.

Reference values

Adult males:2.0-7.5 mg/dl

Adult females: 2.0-6.5 mg/dl

In early pregnancy uric acid levels falls by about one third but rise to non – pregnant levels by term

Children (ages 10-18)

Males: 3.6-5.5 mg/dl significant rise in males ages 12-14 coincides with puberty females: 3.6-4 mg/dl

Elderly Males older than 40 2-8.5 mg/dt

The normal range for urinary uric acid is between 250-750 mg over a 24 Hr Period

An elevated blood uric and level also known as hyperuricemia.It is seen in Gout, Renal disease, and renal failure

Alcoholism

Dehydration

Leukemia and lymphoma

Starvation

Metabolic acidosis

Toxemia of pregnancy

Infectious mononucleosis

Hyperlipidema

Haemolytic anaemia

Excessive cell destruction associated with chemotherapy with chemo therapy and radiation treatment

changes of uric acid concentration during normal pregnancy:

Uric acid concentrations decreased significantly by 8 weeks when compared with pre pregnancy values.

This level maintained until about 24 weeks.

Then the concentrations increased such that by term they were greater than the pre pregnancy values in the majority of patients end remand elevated until 12 weeks after delivery.

	Uric acid
Non pregnant adult	2.5-5.6
First trimester	2.0-4.2
Second trimester	2.4-4.9
Third trimester	3.1-6.3

Uric acid in the first trimester likely approximates preconception uric acid and elevated uric acid may identify women who are predisposed to metabolic syndrome with risk of developing GDM, independent of obesity alternatively uric acid decrease early in pregnancy 80 perhaps

women with elevated uric acid have a poor adaptation to pregnancy leads to adverse pregnancy outcomes such as GDM.

Studies on the association of uric acid and GDM.

Zekai tahir Burak et al:

Studied the relationship between serum uric acid creative albumin gestational diabetes mellitus at the women's Health and Research Hospital, Ankera, Turkey, and found.

Creatinine levels were significantly higher in the diabetic group than in the control group.

Many studies on the association between uric and GDM have been performed.

Zekai Tahir Burak et al:

Studied Relationship between serum uric acid, creatinine, albumin and gestational diabetes mellitus at The Women's Health and Research Hospital, Ankara, Turkey, and found.

Creatinine levels were significantly higher in the diabetic group than in the control group [0.6 +/-0.15 vs. 0.46+/-0.1 mg /dL (53.01+/-13.26

micromol /L vs. 38.01+/- 8.84 micromol /L), P< 0.001]. Uric acid levels were also higher in the diabetic patients, this elevation was statistically significant [4.42+/-1.09 vs 3.1+/-0.84 mg /dL (260.78+/-64.31 micromol /L vs. 231.49+/-49.56 micromol/L), P< 0.001]. There were no differences in mean albumin concentrations or liver function tests.

Title: Hypertension in pregnancy:

Official journal of the international society for the study of Hypertension in pregnancy Volume: ISSN: 1525- 6065 ISO Abbreviation: Publication Date: 2010 Sep studied that High Uric Acid Level during the First 20 Weeks of pregnancy is Associated with Higher Risk for Gestational Diabetes Mellitus and Mild preeclampsia.

Results:

Significant linear association was documented between UA level in the first 20 weeks and the prevalence of GDM and mild preeclampsia. The lowest and the highest prevalence of GDM were found in the UA </=2.4 mEq/L group (6.3%) ab dub the UA> 5.5 mEq/L group (10.5%) (p<0.001), respectively.

Samer Samir Lamey et al

In helipolis Hospital under supervision by prof. Dr. Ali Farid Mohamed ali Professor of Obstetrics &Gynaecology Faculty of Medicine Ain Shams University, 2010 studied the Risk of elevated body mass index in expectation the presence of gestational diabetes mellitus and associated elevated uric acid concentrations.

Lind T, Godfrey KA, et al

Studied the changes in serum uric acid concentrations during normal pregnancy. He found that compared with pre- pregnancy values uric acid concentrations decreased significantly by 8 weeks gestation and this reduced level was maintained until about 24 weeks. Thereafter the concentrations increased such that by term they were greater than the pre-pregnancy values in the majority of patients and remained elevated until at least 12 weeks after delivery.

Simmi Kharb et al:

Studied the relation between Ascorbic acid and uric acid levels in gestational diabetes mellitus and found that Significantly low vitamin C levels were observed in GDM as compared to those in controls (P<0.05). Significantly high serum uric acid levels were observed in GDM as compared to those in controls (P<0.05). Vitamin C and uric acid levels showed a significant negative correlation (r=0.25, P<0.05).

	Control group	Study group
Vit C	1.077± 0.392	0.801± 0.119
Uric acid	3.73± 0.14	5.23± 0.33

MATERIALS AND METHODS

This a prospective study conducted in Tirunelveli Medical College Hospital Tirunelveli. During (July 2015 year July 2016) About 100 antenatal women attending OPD at first trimester were included in the study. After satisfying inclusion & exclusion criteria. They were recruited and informed about the aim of the study. informed consent was got from all patients. Height, weight, BMI was measured Gestational age was confirmed by ultrasonography

Inclusion Criteria:

Antenatal women with gestational age < 12 weeks

Exclusion Criteria:

- Pregnant women > 12 weeks
- Overt DM
- Or who received steroids in any form
- Gout
- Other endocrine disorder
- Chronic renal disease
- Connective tissue disorder

- ❖ H/O thromboembolism
- ❖ Liver disease, Cardio vascular disease

MEASUREMENTOF PLASMAURICACID:

Venous b l o o d s a m p l e was withdrawn from antenatal w o m e n w i t h gestationalage<12weeks.Thesampleswerecentrifugedtose paratethe serum and stored at -70ºC till examined. Uric acid measured using colorimetric assay with detection limit of10mg/dl.Thecoefficientwas0.9%.

SCREENINGFORGDM

All antenatal mothers were followed up around 24-28 weeks for routine GDM screening with 50grams of oral glucose challenge test (GCT). Those antenatal mothers with plasma glucose level after 1hour ≥140mg/dl, these women are considered high risk and are subjected to oral glucose tolerance test (OGTT).

ORAL GLUCOSE TOLERANCE TEST

After about 8 hours of fasting, those antenatal women with positive GCT (≥140mg/dl) are subjected to GTT. Fasting blood glucose

is taken. After which100grams of glucose is taken oral.1hr, 2hr,3hr glucose levels are measured. Patients are considered to have GDM if two or more of the 4 values exceed the following:

Fifth international workshop conference on gestational diabetes-

Fasting - 95mg/dl

1hr - 180mg/dl

2hr - 155mg/dl

3hr - 140mg/dl

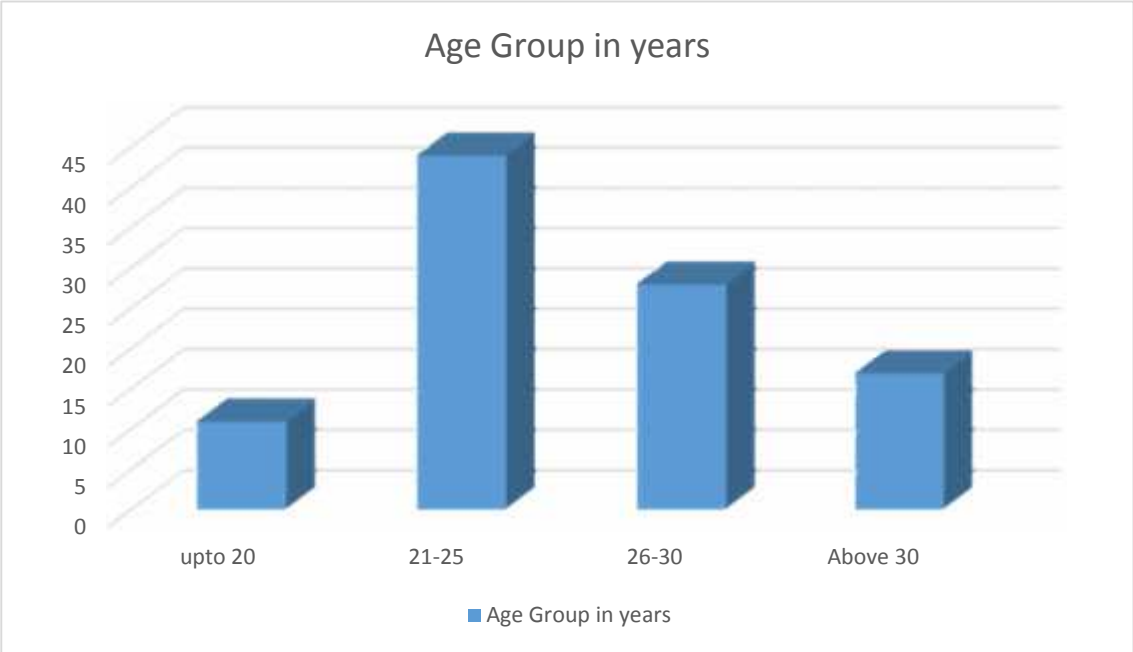
Those antenatal women with positive GTT were admitted as in -patient and further evaluated. These antenatal women were managed with diet and some with both insulin and diet.

RESULTS

TABLE 1: DISTRIBUTION OF PERSONS IN THE STUDY ACCORDING TO AGE

Age in years	Frequency	Percent	Valid percent
20	11	11	11
21-25	44	44	44
26-30	28	28	28
Above 30	17	17	17
Total	100	100	100

FIG 1: DISTRIBUTION OF PERSONS IN THE STUDY ACCORDING TO AGE



In our study, maternal age had no much correlation with the serum uric acid. In our study age between 21-25 years had much frequency constituting 44%.

In a study by S. Katherine LAUGHON et al, the mean maternal age and gestational age at sampling decreased slightly with increasing uric acid quartile.

Above table shows the distribution of persons according to age upto 20 years it is about 11%, 21-25years of age - 44%, in the age group of 26-30 28% above 30 years it is about 17%.

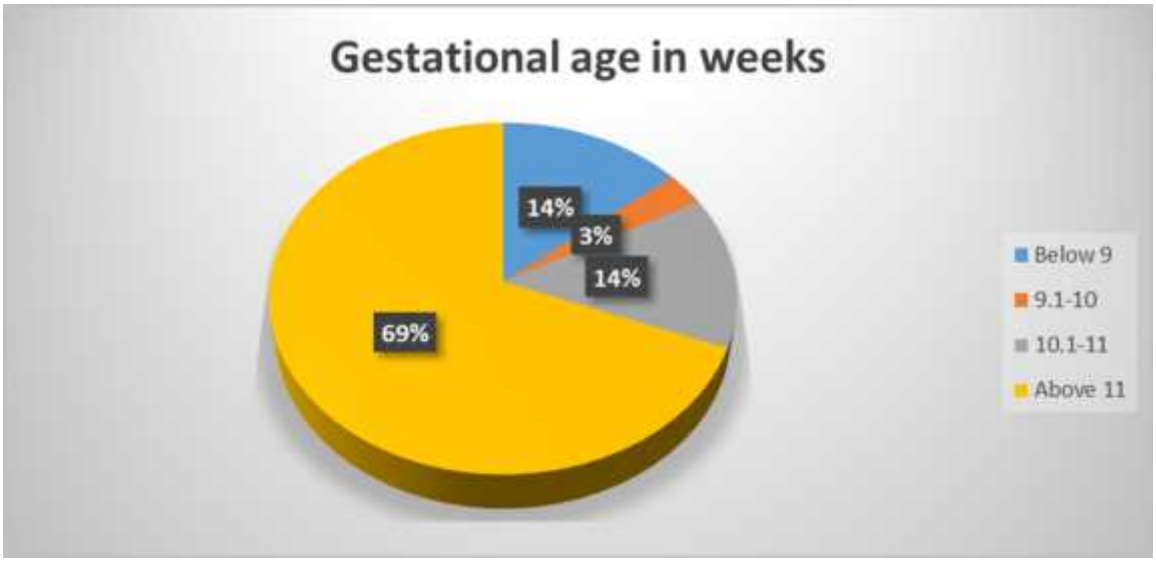
TABLE 2: DISTRIBUTION OF PERSONS IN THE STUDY ACCORDING TO PARITY

Parity	Numbers	Percentage
Primi	**53**	**53**
Multi	**47**	**47**
Total	**100**	**100**

TABLE 3: Distribution of persons with gestational age in weeks

Weeks in pregnancy		Frequency	Percent	Valid Percent
	Below 9	**14**	**14**	**14**
	9.1-10	**3**	**3**	**3**
	10.1-11	**14**	**14**	**14**
	Above 11	**69**	**69**	**69**
	Total	**100**	**100**	**100**

FIG 2: GESTATIONAL AGE IN WEEKS



In our study the frequency is high around above 11 weeks. And this had no much correlation within the first trimester.

Table 4: Distribution of maternal age with elevated uric acid

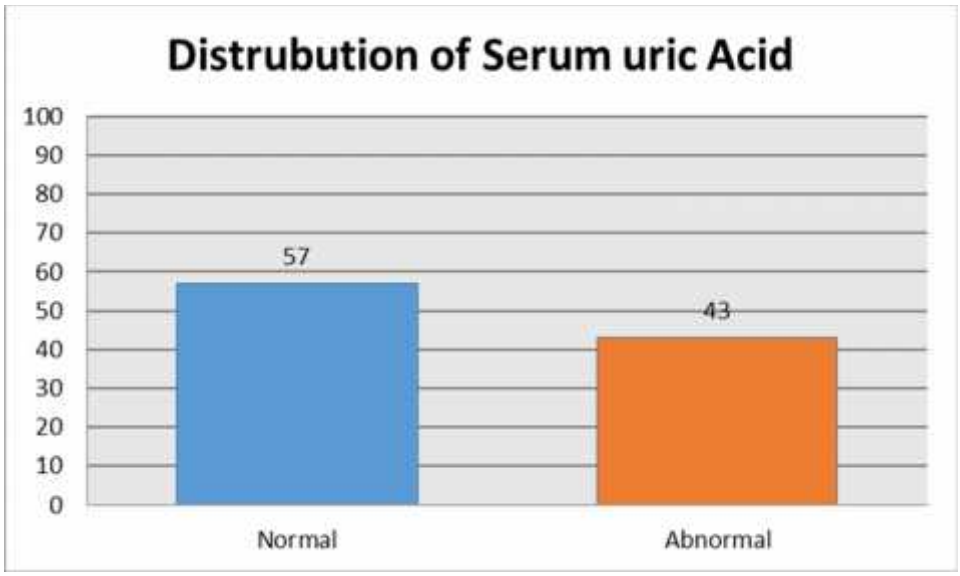
Age	Number(elevated uric acid)
Upto 20	5
21-25	19
26-30	15
>30	4
Total	**43**

Among total 43 patients with elevated uric acid 19 of them from 21-25 years of age 15 of them 26-30 years of age.

TABLE 5 : DISTRIBUTION OF SERUM URIC ACID

	Frequency	Percent	Valid Percent	Cumulative Percent
Normal	57	57	57	57
Abnormal	43	43	43	100
Total	100	100	100	

FIG 3: DISTRIBUTION OF SERUM URIC ACID

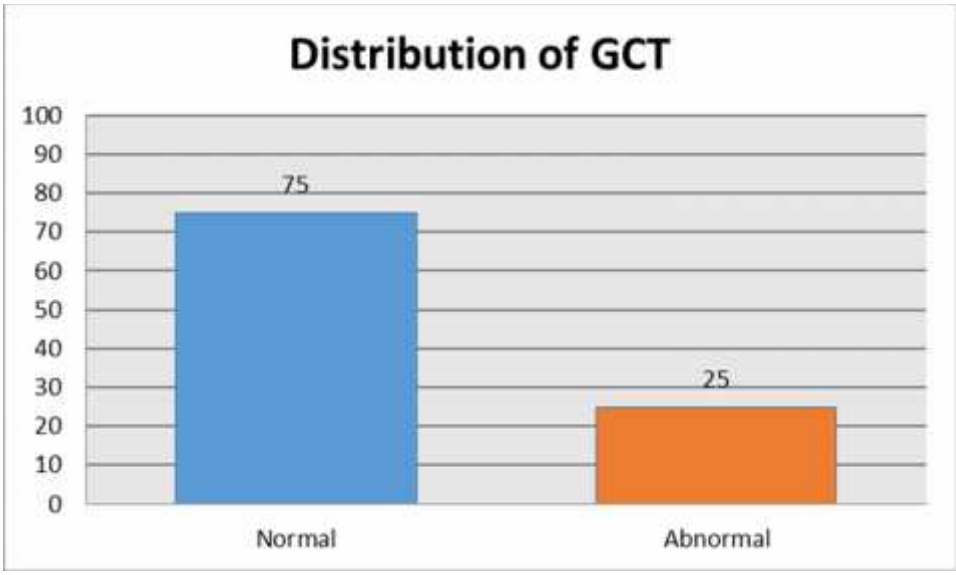


This table shows the distribution of serum uric acid among the total 100 antenatal patients. 57 patients had normal uric acid constituting about 51% and 43 patients had elevated uric acid constituting about 43%

TABLE 6: DISTRIBUTION OF GLUCOSE CHALLENGE TEST

	Frequency	**Percent**	**Valid Percent**	**Cumulative Percent**
Normal	75	75	75	75
Abnormal	25	25	25	100
Total	100	100	100	

FIG 4:DISTRIBUTION OF GLUCOSE CHALLENGE TEST

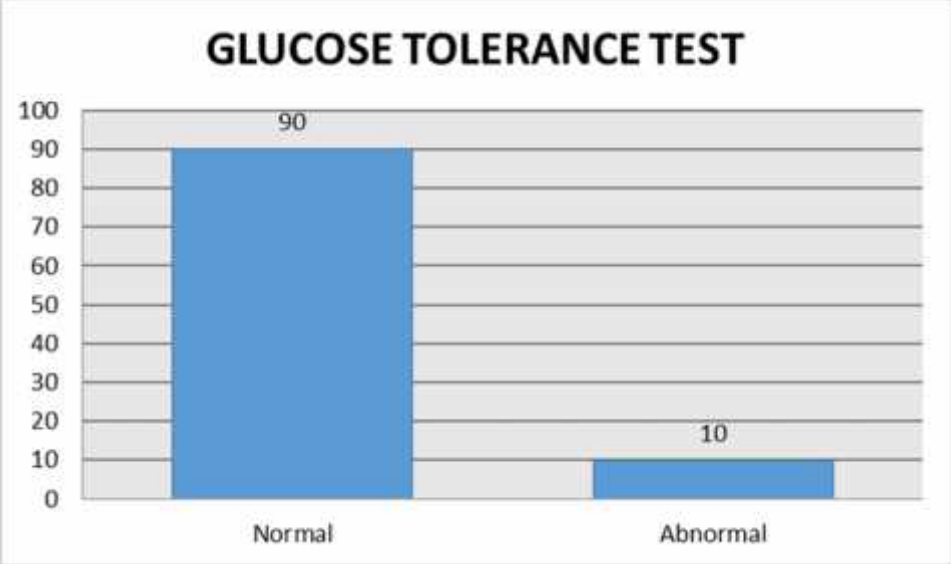


This above table shows the distribution of OCGT. GCT was normal in 75 patients, constituting 75% and GCT was positive in 25% constituting 25%.

TABLE 7: GLUCOSE TOLERANCE TEST

	Frequency	**Percent**	**Valid Percent**	**Cumulative Percent**
Normal	90	90	90	90
Abnormal	10	10	10	100
Total	100	100	100	

FIG 5: GLUCOSE TOLERANCE TEST



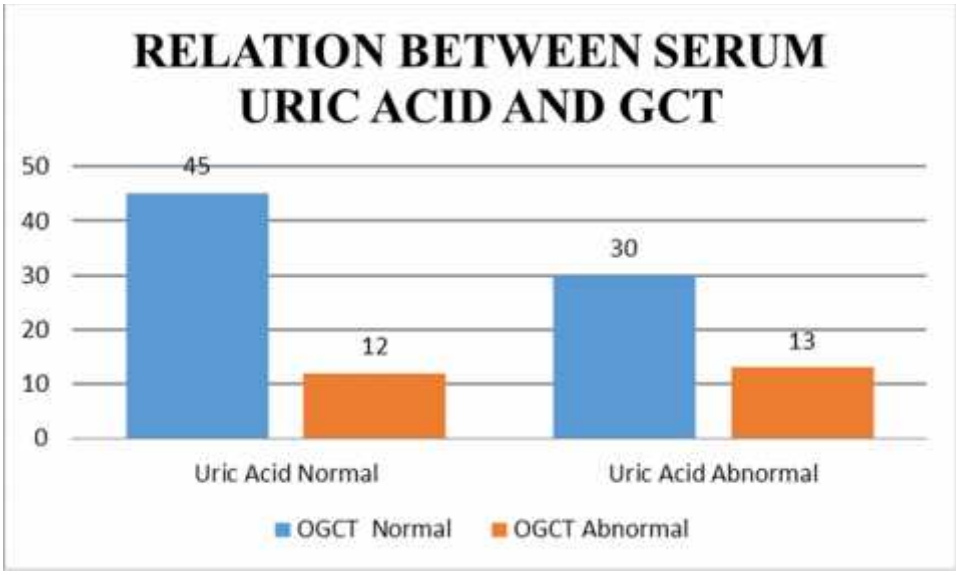
This above table infers that 10 patients had GTT constituting 10% and 90 patients negative constituting 90%.

TABLE 8: SERUM URIC ACID * GCT CROSS TABULATION

	OGCT	
Uric Acid	**OGCT Normal**	**OGCT Abnormal**
Uric Acid Normal	45	12
Uric Acid Abnormal	30	13

	N	Mean	Std. Deviation	Correlation coefficient	P value
URIC	100	3.50	1.21	0.209	0.036
OGCT	100	114.90	31.79		

FIG 6: RELATION BETWEEN SERUM URIC ACID AND GCT



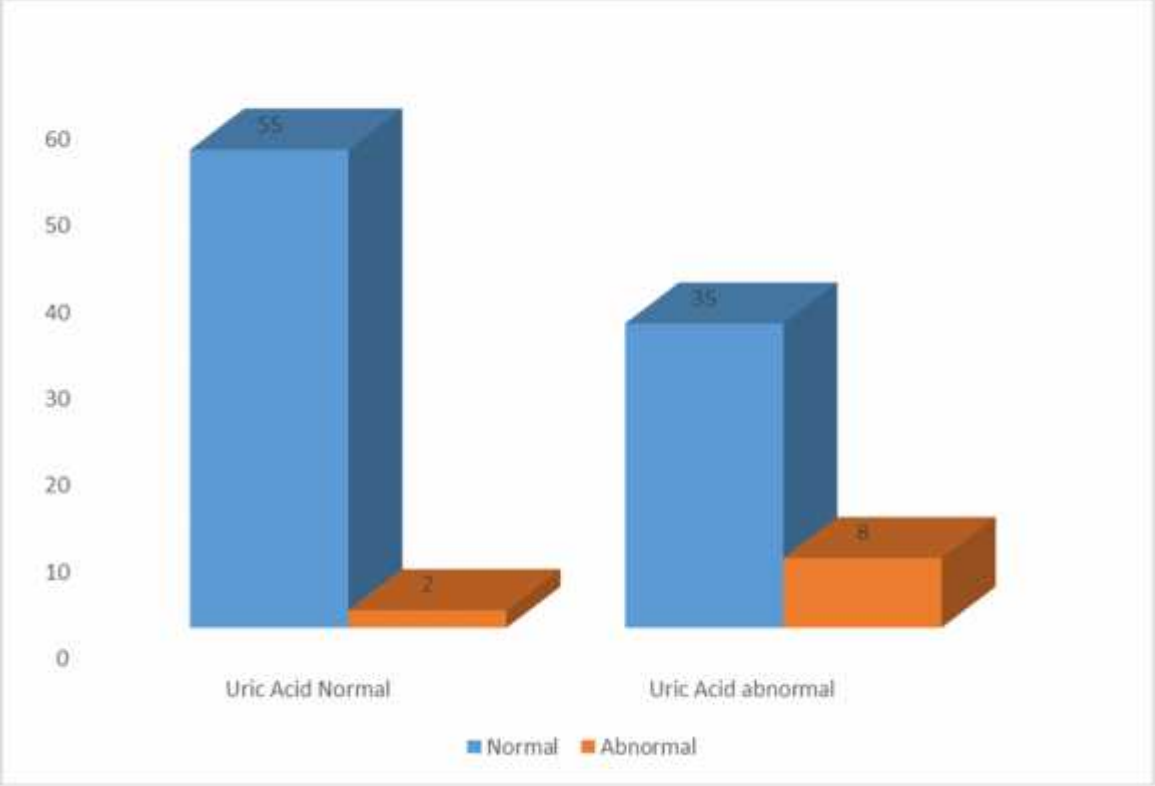
In our study of the total patients 43 with elevated uric acid, 13 patients had positive GCT – constituting 37%. and those with normal uric acid of 57 patients 12 were positive for GCT (21%).

TABLE 9: SERUM URIC ACID * GTT CROSS TABULATION

Uric Acid	**GTT**	
	Normal	**Abnormal**
Normal	55	2
Abnormal	35	8
Total	**90**	**10**

Uric Acid	GTT		P value
	Normal	Abnormal	
Normal	55	2	0.041
Abnormal	35	8	

FIG 7: RELATIONSHIP BETWEEN SERUM URIC ACID AND GTT



In our study among the 43 patients with elevated uric acid, 8 patients were positive for GTT. And the remaining 35 negative for GTT. And among the 57 patients with normal uric acid only 2 were GTT Positive. Hence elevated uric acid in the first trimester strongly associated with GTT (P valve < 0.05)

TABLE 10: DISTRIBUTION OF PATIENTS DIAGNOSED GDM ACCORDING TO PARITY

PARITY	TOTAL NO OF PATIENTS	NO OF PATIENTS WITH GDM
PRIMI	53	5
MULTI	47	5

TABLE 11: DISTRIBUTION OF PATIENT DIAGNOSED AS GDM ACCORDING TO AGE

AGE	NO OF PATIENT DIAGNOSED AS GDM
UPTO 20	0
21-25	4
26-30	3
>30	3
TOTAL	10

TABLE 12: CROSS TABULATION OF ELEVATED URICACID WITH DEVELOPMENT OF GDM

NO OF PATIENT	OGCT		GTT POSITIVE
	+VE	_VE	
URIC ACID ABNORMAL (N 43)	13	20	8
URIC ACID NORMAL (N 57)	12	45	2
Total	25	65	10

TABLE 13: DESCR`IPTIVE STATISTICS

	N	Mean	Std. Deviation	P value
AGE	100	25.36	4.77	
HT	100	151.44	7.45	
WT	100	50.66	7.03	
GA_WEEK	100	12.31	2.04	
URIC	100	3.50	1.21	0.426
OGCT	100	114.90	31.79	<0.0001
BMI	100	22.19	3.37	

	N	Mean	Std. Deviation	Correlation coefficient	P value
URIC	100	3.50	1.21	0.179	0.074
BMI	100	22.19	3.37		

TABLE 14: RELIABILITY OF THE TEST SERUM URIC ACID IN PREDICTING GDM

Sensitivity	Specificity	Positive predictive Value	Negative predictive Value	Odds ratio
80%	69%	18.65	96.4%	6.2

In a similar study by S. Katherine LAUGHON et al, his hypothesis was the mean maternal age and gestational age at sampling decreased slightly with increasing uric acid quartile. Maternal pre- pregnancy BMI increased linearly with increasing uric acid quartile ($p<0.01$ for trend and was associated with uric acid with an r^2 of 0.16 ($p<0.001$)

TABLE 15: COMPARISON

	Our Study	S.Katherine laughon et al
Positive predictive value	**18.6 %**	**12**
Negative predictive value	**96.4%**	**96.7**
Odds ratio	**6.2 %**	**3.9***

DISSCUSSION

Pregnancy induces progressive changes in maternal carbohydrate metabolism. As pregnancy advances insulin resistance and diabetogenic stress due to placental hormones necessitate compensatory increase in insulin secretion. When this compensation is inadequate gestational diabetes develops

It is possible that the association of uric acid with insulin resistance is causal. Two mechanisms have been hypothesized by which uric acid can cause insulin resistance. Nakagawa et al. proposed that uric acid causes endothelial dysfunction and decreases nitric oxide production by the endothelial cell. In animals, insulin's action on glucose uptake into cells in the skeletal muscle and adipose tissue is dependent on nitric oxide. Thus, decreases in nitric oxide lead to decreased glucose uptake and the development of insulin resistance. Another mechanism by which uric acid may induce insulin resistance may be that uric acid causes inflammation and oxidative stress in adipocytes, which is a contributor to the development of metabolic syndrome in mice.

In our prospective study 100 antenatal women were included belonging to first trimester, who were attendees of Govt. tirunelveli medical college In our study of the total 100 antenatal 10 were developed GDM. Out of 10 8 had elevated serum uric acid in first trimester, which constitute about 16.7(

% within in GTT).And among 2 GDM mothers with normal serum uric acid constitute about 3(% within GTT).with p value <0.001)

In our study all antenatal women undertook glucose challenge test (GCT), more of a screening test. Of the normal uric acid GCT was positive among

12 mothers(constituting 21%).Of the elevated serum uric acid GCT was positive among 13% mothers(constituting 66.7%).With significant p< 0.001

Though uric acid was strongly associated with body mass index, the risk of gestational diabetes was increased among women with elevated first trimester uric acid independent of BMI.

Our findings are consistent with the association of uric acid with insulin resistance in the non-pregnant population.[1] In a large cross-sectional study of 53,477 non-pregnant adults, serum uric acid was positively correlated with fasting serum glucose and insulin resistance, as well as features of the

metabolic syndrome, including waist circumference, low HDL cholesterol, hypertriglyceridemia, hypertension and fasting glucose ≥

110 mg/dl.

A study by Di Cianni et al. in which serum uric acid was measured at a median of 16 months postpartum in women who had pregnancies complicated by gestational diabetes. Uric acid was significantly higher in women with metabolic syndrome (4.8 ± 1.2 mg/dl) versus women without metabolic syndrome (4.1 ± 0.8, $p<0.01$), independent of BMI, and metabolic syndrome is a known risk factor for developing type 2 diabetes.

We did not measure creatinine in order to adjust for glomerular filtration rate (GFR), but the majority of women would be expected to have normal excretion since we excluded women with prior diabetes, hypertension, kidney disease or major medical problems

Hyperuricemia has also been demonstrated to be a risk factor for developing type 2 diabetes.

This study demonstrates a striking association between first trimester uric acid and risk of developing gestational diabetes. Women who have a pregnancy complicated by gestational diabetes have up to a 50% chance of developing type 2 diabetes in their lifetime. It would be interesting to know whether these were the women with elevated uric acid in the first trimester.

The relationship of uric acid elevation in early pregnancy does indicate that metabolic state may affect adverse pregnancy outcomes. With the increase in both metabolic syndrome and obesity, more women are entering pregnancy with these conditions. It is possible that of the women who develop GDM, those with elevated first trimester uric acid are the women who are at risk to develop type 2 diabetes, and this warrants future investigation.

Thus we postulate that elevated first trimester serum uric acid helps in the prediction of gestational diabetes mellitus and also identify those at risk of developing type II Diabetes mellitus & follow up; also to counsel the patient about the short term and long term outcomes.

CONCLUSION

The objective of implementing an antenatal screening test for GDM is to identify pre-symptomatic women who will subsequently develop complications of pregnancy and implement efficacious treatment to reduce morbidity and mortality. Currently, complications of pregnancy due to GDM are not diagnosed until mid-late gestation.

It is important to recognize that by the time GDM is diagnosed in the late second or early third trimester of pregnancy, the 'pathology' is probably established and that reversal of the potential adverse perinatal outcomes may be limited. Many health professionals advocate

the need for an earlier diagnostic/predictive test for GDM, one among them is "THE FIRST TRIMESTER SERUM URIC ACID".

A pregnant woman with high risk factors as marked obesity, strong family history of Type II DM, previous history of GDM, impaired glucose metabolism or glucosuria, History of neonatal death, History of fetal macrosomia, along with > 3.6 mg/dl is at risk of developing GDM.

The use of FIRST TRIMESTER SERUM URIC ACID as a predictor of GDM is simple, inexpensive, non invasive and easy to perform. This can be used as a screening test for the prediction of GDM.

Hence in routine antenatal care with predictive test like first trimester serum uric acid can be applied as a screening test for all women so we can predict GDM & diagnosed in time.

BIBLIOGRAPHY

1)Modan M,Halkin H,Karasik A. Elevated uric acid –a facet of hyperinsulinaemia.Diabetologia 1987;30:713-8(PubMed)

2)Nakagawa T,Tuttle KR, Short RA,Jonson RJ. Hypothesis:fructose induced hyperuricemia as a causal mechanism for the epidemic of the metabolic syndrome.Nat clin prac Nephrol.2005;1:80-6(PubMed)

3)Masuo k,Kawaguchi ,Mikami H, OGIHARA T.Serum uric acid and plasma norepinepherine concentrations predict subsequent weight gain and blood pressure elevation.Hypertension,2003;42:474-80.

4)Choi HK ,Ford ES ,Prevalence of metabolic syndrome in individuals with hyperuricemia.Am J med.2007;120:442-7.

5)Coutino Tde A,Turner ST,Peyser PA,Bielak LF,Sheedy PF,2nd ,Kullo IJ.Associations of serum uric acid with markers of inflammation,metabolic syndrome and subclinical conorary atherosclerosis.Am J Hypertension ;2007;20:83-9

6) Dehghan A, van Hoek M ,Sijbrands EJ A, High uric acid as a novel risk factor for type 2 diabetes.Diabetes care 2008;31:361-2

7)Weisz B,Cohen O,Homko CJ,Schiff E,Sivan E.Elevated serum uric acid levels in gestational hypertension are correlated with insulin resistance.

8)Gungor ES ,Danisman N,Mollamahmutoglu L.Relationship between serum uric acid,creatine clearance ,albumin and gestational diabetes milletus.Clin Chem lab Med 2006;44:974-7

9)Anastasiou E,Lekakis JP,Alevizaki M,et al.Impaired endothelium-dependent vasodilatation in women with previous gestational diabetes.Diabetes Care 1998;21:2111-5

10)Carpenter MW,Couston DR.Criteria for screening tests for gestational diabetes.Am J Obstet Gynaeco.1982:144:768-73

11)Dooley SL,Metzer BE,Cho N,Liu K.The influence of demographic and phenotypic heterogeneity on the prevalence of gestational diabetes milletus.Int J Gynaecol Obstet.1991;35:13-8.

12). Powers RW,Bodnar LM,Ness RB,et al.Uric acid concentrations among preeclamptic women with gestational hyperuricemia at delivery .Am J Obstet gynaec.2006;194:160.

13)Yoo TW,Sung KC,Shin HS,et al.Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome.Circ J.2005;69:928-33.

14)Nakanishi N,Okamoto M,Yoshida H,Matsuo Y,Suzuki K.Serum uric acid and risk of development of hypertension and impaired fasting glucose or TypeII Diabetes in Japanese male office workers.Eur J Epidemiol.2003;18:523- 30

15)Lind T,Godfrey KA,Otun H,Philips PR.Changes in serum uric acid during normal pregnancy.Br J Obstetr Gynaecol .1984;91:128-32.

16)Feig DI ,Kang DH,Johnson RJ.Uric acid and cardiovascular risk.N Engl J Med.2008;359:1811-21

17)Cook S,Hugli O,Egli M,et al.Clustering of cardiovascular risk factors mimicking the human metabolic syndrome X in Enos null mice.Swiss Med Wkly.2003;133:360-3

18)Roy D,Perreault M,Marette A.Insulin stimulation of glucose uptake in skeletal muscles and tissues in vivo is NO dependent.Am J Physiol.1998;274:E692-9

19)Sautin YY,Nakagawa T,Zharikov S,Johnson RJ.Adverse effects of the classic antioxidant uric acid in adipocytes :NADPH oxidase-mediated oxidative/nitrosative stress.Am J Physiol.2007;293:C584-96

20) Furukawa S,Fujita T,Shimbukuro M,et al.C-reactive protein and metabolic syndrome in women with previous gestational diabetes .Diabetes Metab Res Rev.2007;23:135-40.

21) Di Cianni G,Lencioni C,Volpe L,et al.Increased oxidative stress in obesity and its impact on metabolic syndrome.J Clin Invest.2004;114:1752-61

22) Thomas R Moore, MD et al. Diabetes Mellitus and Pregnancy. Med/2349 at eMedicine. Version: Jan 27, 2005 update.

23) Metzger BE, Coustan DR (Eds.). Proceedings of the Fourth International Work-shop-Conference on Gestational Diabetes Mellitus. Diabetes Care 1998; 21 (Suppl. 2): B1–B167.

24) BECKETT, A.G. &LEWIS, J.G. (1960). Gout and serum uric parameters in diabetes mellitus. Quarterly Journal of Medicine, 29, 443.

25) BONER,G. &RIESELBACK, R.E. (1974).The effect of glucose upon reabsorptive transport of urate by the kidney.Advances in Experimental Medicine and Biology, 41, 781.

26) HERMAN, J.B. & GOLDBOURT, U.(1982).Uric acid&Diabetes :observations in a population study. Lancet, ii, 240.

27) HERMAN, J.B., MEDALIE, J.H. & GOLDBOURT, U.Diabetes, prediabetes and uricemia. Diabetologia, 12, 47.

28) Wein, P., Dong, Z. G., Beischer, N. A. & Sheedy, M. T. (1995). Factors predictive of recurrent gestational diabetes diagnosed before 24 weeks' gestation. Am J Perinatol, Vol.12, No.5, pp. 352-356, issn 0735-1631

29) Wein, P. & Beischer, N. A. (2000). Observed increase in prevalence of gestational diabetes is real. Am J Obstet Gynecol, Vol.182, No.4, pp. 992-

993, issn 0002-
9378

30) Williams, M. A., Qiu, C., Muy-Rivera, M., Vadachkoria, S., Song, T. & Luthy, D. A. (2004). Plasma adiponectin concentrations in early pregnancy and subsequent risk of gestational diabetes mellitus. J Clin Endocrinol Metab, Vol.89, No.5, pp. 2306-2311, issn 0021-972X

31) Savvidou, M., Nelson, S. M., Makgoba, M., Messow, C. M., Sattar, N. & Nicolaides, K. (2010). First-Trimester Prediction of Gestational Diabetes Mellitus: Examining the Potential of Combining Maternal Characteristics and Laboratory Measures. Diabetes, Vol.59, No.12, pp. 3017-3022, issn

0012- 1797

32) Ryan, E. A. (2011). Diagnosing gestational diabetes. Diabetologia, Vol.54, No.3, pp. 480-486, issn 1432-0428

33) Sacks, D. A., Chen, W., Wolde-Tsadik, G. & Buchanan, T. A. (2003). Fasting plasma glucose test at the first prenatal visit as a screen for gestational diabetes. Obstet Gynecol,Vol.101, No.6, pp. 1197-1203, issn

0029- 7844

34) The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. (2008). College statement, C-Obs 7, Diagnosis of gestational diabetes mellitus. Melbourne: authors.

35)Tomazic, M., Janez, A., Sketelj, A., Kocijancic, A., Eckel, J. & Sharma, P. (2002). Comparison of alterations in insulin signaling pathway in adipocytes from type 2 diabetic pregnant women and women with gestational diabetes mellitus. Diabetologia, 45, 502-508

36) Tuffnell, D., West, J., & Walkinshaw, S. (2005). Treatments for gestational diabetes and impaired glucose tolerance in pregnancy. Cochrane Database of Systematic Reviews, 1.89

37) Tuffnell, D., West, J., & Walkinshaw, S. (2005). Time to screen for, and treat, gestational diabetes. British Journal of Obstetrics and Gynaecology,

113, 3-4.

38) Tuomilehto, J., Lindstrom, J., Eriksson, J. & Valle, T. (2001). Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. The New England Journal of

Medicine, 344, (18), 1343-11350.

PROFORMA

ASSOCIATION OF FIRST TRIMESTER URIC ACID A PREDICTOR OF GDM

OUTCOME.

NAME : AGE: I.P. NO. : SOCIAL

STATUS : BOOKED/UNBOOKED: LMP :

G P L A

EDD : GESTATIONAL AGE :

DATE OF USG : OBSTETRIC

HISTORY : MATERNAL

ILLNESS : GENERAL

EXAMINATION :

HT. WT. PULSE: BP: TEMP:

ANAEMIA: EDEMA: CVS: RS:

OBETETRIC EXAMINATION

P/A :

USG

BLOOD INVESTIGATIONS-

- SERUM URIC ACID(<12 weeks)
- GCT (Glucose challenge test) - 24- 28 weeks.
- GTT (Glucose tolerance test).

S.No	Name	Age	OP No	Ht	ht in metre	Wt	BMI	GA Weeks	OBS Code	Uric Acid	OGCT	GTT
1	Essaki	21	61901	153	1.53	61	26.0584	16	Primi	**5.2**	**189**	**80/190/188**
2	Perumal	37	61911	154	1.54	60	25.2994	14	G3P2L2	3.2	**150**	N
3	Prabakaran	32	62403	145	1.45	55	26.1593	12	Primi	2.2	**166**	N
4	Utchimagali	37	16633	165	1.65	56	20.5693	14	G5P1L3	**5**	**203**	**120/190/150**
5	Mala	23	35217	148	1.48	50	22.8269	16	G2A1	2.7	116	N
6	Syed	23	21619	165	1.65	71	26.079	9	G2P1L1	**5.2**	**143**	**F147/203/170**
7	Shanthi	40	61971	156	1.56	65	26.7094	14	C2P1L1	2.5	60	N
8	Anitha	23	61900	149	1.49	43	19.3685	12	C2P1L1	**4.1**	90	N
9	Jesumariyal	28	57483	149	1.49	49	22.0711	9	Primi	3.2	127	N
10	Uma Mahesh	37	50189	148	1.48	60	27.3923	9	G2P1L1	**4.6**	**156**	**88/201/166**
11	Pushponai	23	56200	155	1.55	49	20.3954	16	G3A2	**5**	71	N
12	Muthu mari	19	47836	140	1.4	44	22.449	14	Primi	2.2	60	N
13	Valamath	25	57179	152	1.52	44	19.0443	12	Primi	**5.1**	129	N
14	Seetha	22	57246	153	1.53	45	19.2234	11	Primi	2.8	**149**	**143/187**
15	Jennathnish	27	57143	157	1.57	65	26.3702	14	G2P1L1	**4.7**	**140**	N
16	Subbulakshmi	21	43036	165	1.65	57	20.9366	11	G2A1	**4.2**	82	N
17	Ramalakshmi	30	57067	160	1.6	58	22.6563	16	C3P1L1	2.6	86	N
18	Kamalesh	24	56401	148	1.48	45	20.5442	12	C2P1L1	2.6	70	N
19	Rajammal	36	56817	153	1.53	54	23.0681	13	C2P1L1	2.1	**147**	**83/196/169**
20	Maheswari	25	54315	146	1.46	49	22.9874	14	Primi	2	81	N
21	Rajkala	26	53557	154	1.54	50	21.0828	16	C3P2L2	**3.6**	128	N
22	Usha	25	43214	150	1.5	46	20.4444	11	Primi	**4.4**	86	N
23	Subbulakshmi	21	43036	165	1.65	57	20.9366	14	Primi	**4.2**	82	N
24	Arumugam	23	43034	158	1.58	45	18.026	11	C2A1	**3.8**	102	N
25	Muppidathi	20	43038	149	1.49	44	19.8189	13	Primi	2.8	70	N
26	Mani mala	21	43020	165	1.65	63	23.1405	14	C2P2L1	3.2	129	N
27	Marishwari	27	50261	155	1.55	52	21.6441	10	C3P2L2	**3.6**	77	N
28	Seetha	23	455299	120	1.2	49	34.0278	12	Primi	**4.4**	113	N
29	Shanmuga priya	21	34967	155	1.55	45	18.7305	12	Primi	2.2	92	N
30	Mahalakshmi	23	30759	147	1.47	37	17.1225	13	Primi	2.8	114	N
31	Anandhi	31	49845	150	1.5	41	18.2222	14	C2P1L1	2	**141**	N
32	Essakiammal	20	49658	157	1.57	50	20.2848	9	Primi	**4.1**	60	N

S.No	Name	Age	OP No	Ht	ht in metre	Wt	BMI	GA Weeks	OBS Code	Uric Acid	OGCT	GTT
33	Elizabeth Rani	24	49744	155	1.55	48	19.9792	9	C3P1L1	2.5	100	N
34	Maharaja	21	49784	154	1.54	52	21.9261	11	C2P1L1	3.4	120	N
35	Palaniana	19	47037	152	1.52	55	23.8054	14	Primi	**5.6**	100	N
36	Petchiammal	23	19536	145	1.45	45	21.4031	10	C3P2L1	3.2	116	N
37	Kalaselvi	21	36746	157	1.57	46	18.662	16	Primi	**5.8**	88	N
38	Chitra devi	23	45529	120	1.2	49	34.0278	9	Primi	**4.4**	113	N
39	Amutha	29	31963	155	1.55	61	25.3902	12	C2P1L1	3.4	101	N
40	Benezir	20	45584	147	1.47	54	24.9896	11	Primi	2.7	109	N
41	Annal	26	45557	145	1.45	55	26.1593	15	C3P1L2	3.2	102	N
42	Syed Ali	36	45923	164	1.64	58	21.5645	14	C2P1L1	**4.8**	125	N
43	Kaneswari	32	405389	151	1.51	50	21.9289	11	G2PL1	3	**193**	N
44	Essaki selvi	21	45364	154	1.54	52	21.9261	9	Primi	2.9	**147**	N
45	Ambitha	28	45367	149	1.49	55	24.7737	14	C3P2L2	3.2	63	N
46	Poosomd	33	32665	151	1.51	51	22.3674	16	Primi	3	**140**	N
47	Mani mala	27	370414	155	1.55	51	21.2279	12	Primi	**4.2**	106	N
48	Pushpa latha	22	40521	146	1.46	40	18.7652	10	Primi	**3.6**	90	N
49	Ambika	29	16607	146	1.46	47	22.0492	13	C2P1L1	3	105	N
50	Lakshmi	19	40401	150	1.5	38	16.8889	12	Primi	2.7	123	N
51	Mariammal	26	38402	153	1.53	45	19.2234	9	Primi	3.3	105	N
52	Muthu mari	24	25890	148	1.48	42	19.1746	13	C2P1L1	2.1	128	N
53	Thanga selvi	31	87796	152	1.52	59	25.5367	12	C2P1L1	**6.5**	60	N
54	Ayyand	37	35430	139	1.39	55	28.4664	14	C2P1L2	2.3	119	N
55	Myder	28	32853	156	1.56	49	20.1348	9	Primi	2.6	**141**	**120/214/193**
56	Seetha lakshmi	24	32344	154	1.54	65	27.4077	12	Primi	**5.6**	**199**	N
57	Maharani	27	32606	150	1.5	50	22.2222	13	C2P1L1	2.1	60	N
58	Bala Murugesh	28	32486	160	1.6	58	22.6563	11	Primi	**5.3**	**146**	N
59	Jeyalakshmi	23	51903	152	1.52	39	16.8802	9	Primi	2	98	N
60	Devi	23		145	1.45	48	22.83	14	C2P4	**3.6**	122	N
61	Essakiammal	19	23194	151	1.51	44	19.2974	12	Primi	**5.2**	**140**	N
62	Meena	20	22985	160	1.6	42	16.4063	10	Primi	3.3	88	N
63	Sathi Rajeswari	21	22553	156	1.56	60	24.6548	12	Primi	**3.8**	99	N
64	Gomathi	22	22970	148	1.48	50	22.8269	13	C2P1L1	3.4	100	N

S.No	Name	Age	OP No	Ht	ht in metre	Wt	BMI	GA Weeks	OBS Code	Uric Acid	OGCT	GTT
65	Meena	20	22368	160	1.6	48	18.75	14	C2P1L1	3.3	108	N
66	Esthar	26	21556	157	1.57	57	23.1247	9	C2P1L2	**4.4**	83	N
67	Dhendalesh	30	22302	147	1.47	36	16.6597	9	Primi	2.7	113	N
68	Maharasi	18	22201	148	1.48	56	25.5661	13	Primi	**5.2**	118	N
69	Rajalatha	28	27928	154	1.54	48	20.2395	14	Primi	**7.2**	**140**	**130/279/160**
70	Muthu Selvi	21	27900	145	1.45	53	25.2081	15	Primi	**4.7**	**142**	N
71	Muppidathi	29	17238	155	1.55	45	18.7305	12	C4P3L3	2.7	121	N
72	Poovarasu	28	17239	150	1.5	43	19.1111	14	Primi	2	118	N
73	Mari selvi	21	17306	149	1.49	52	23.4224	11	Primi	2	60	N
74	Parvathy	27	17329	138	1.38	48	25.2048	13	Primi	2	108	N
75	Anadha Lakshmi	22	17314	145	1.45	40	19.025	14	Primi	1.9	98	N
76	Muthu Selvi	28	13975	147	1.47	65	30.0801	9	C2P1L1	**3.9**	120	N
77	Karpaga valli	24	17410	148	1.48	48	21.9138	12	C2P1L1	2.2	95	N
78	Anadha Lakshmi	22	15819	162	1.62	46	17.5278	12	Primi	**5.7**	**158**	**87/230/180**
79	Arumugam	27	96781	160	1.6	54	21.0938	13	Primi	**4.8**	106	N
80	Malathy	21	15260	157	1.57	50	20.2848	14	Primi	1.9	**149**	N
81	Karthiga	29	15167	150	1.5	52	23.1111	9	C3P2L1	2.1	82	N
82	Vijayalakshmi	26	15108	160	1.6	58	22.6563	13	C3P2L1	2.2	**140**	N
83	Aorthy	20	12345	140	1.4	43	21.9388	9	Primi	2	100	N
84	Devika	28	12665	151	1.51	55	24.1217	13	C4P1L1A1	**5.2**	**196**	**119/231**
85	Karpagam	20	15187	148	1.48	43	19.6311	9	Primi	**5.3**	121	N
86	Ragavali	24	15170	145	1.45	41	19.5006	13	C2P1L1	**3.9**	**149**	N
87	Petchiammal	21	14345	155	1.55	42	17.4818	11	Primi	2.5	81	N
88	Sornam	27	12386	158	1.58	52	20.83	14	C3P2L2	2	**157**	N
89	Devi	23	10074	146	1.46	43	20.1726	13	C2P1L1	2.7	122	N
90	Lakshmi	26	23076	160	1.6	56	21.875	14	Primi	3	101	N
91	Priya	23	22070	154	1.54	52	21.9261	11	Primi	3	98	N
92	Anadhi	24	21086	146	1.46	58	27.2096	16	C2P1L1	3	92	N
93	Maharasi	30	28072	156	1.56	52	21.3675	12	Primi	**4**	90	N
94	Ponnuthai	22	32086	152	1.52	48	20.7756	11	Primi	2.8	126	N
95	Puthiyaselvi	28	32086	150	1.5	52	23.1111	14	C2P1L1	**3.8**	118	N
96	Dhiya	23	32044	142	1.42	48	23.8048	13	Primi	**3.8**	120	N

S.No	Name	Age	OP No	Ht	ht in metre	Wt	BMI	GA Weeks	OBS Code	Uric Acid	OGCT	GTT
97	Rajevalli	24	28156	148	1.48	55	25.1096	12	Primi	3.2	128	N
98	Veni	26	21260	156	1.56	56	23.0112	14	C2P1L1	**5.8**	118	N
99	Rajalakshmi	24	20086	152	1.52	50	21.6413	11	Primi	2.3	120	N
100	selvi	30	10856	142	1.42	56	27.7723	12	primi	**3.9**	138	N